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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/471,523	12/23/1999	Richard B. van Breemen	21726/90386	7519

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Barnes & Thornburg
2600 Chase Plaza
10 South LaSalle Street
Chicago, IL 60603

EXAMINER	
PRASTHOFER, THOMAS W	
ART UNIT	**PAPER NUMBER**
1627	12

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
file copy	09/471,523	BOLTON ET AL.	
	Examiner	Art Unit	
	Thomas W Prasthofer	1627	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Status of the Application

Receipt is acknowledged of a response to a restriction requirement on 12 September 2001 (Paper No. 11)

Status of the Claims

Claims 1-12 are pending in the present application and are being examined on their merits.

Withdrawn Rejections

1. All outstanding rejections of claims 1-11 are withdrawn.

New Grounds of Rejection/Objection

Objections to the Claims

2. Claim 10 is objected to because it appears that the word "whereas" in claim 10 should be replaced by the word "wherein."

3. Claim 8 is objected to because the word "and" is missing between "interaction" and "control" in claim 8, line 6.

Claims Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 recites a kit that comprises "*a set of standard solutions with predetermined characteristics.*" There are no limitations whatsoever on the number of standards, their compositions, or their "*predetermined characteristics*." Consequently, the claim encompasses any number of solutions of any composition with any "*predetermined characteristics*," which reads on all solutions that can exist. Applicants are required to reasonably convey, to one skilled in the relevant art that, the inventors had possession of the claimed (i.e. the full scope of the invention) at the time that the invention was made. Applicants provide a small number of drugs and the predetermined characteristics of glutathione adduct formation, absorption into a single cell type, and catabolism by cytochrome P450 in the specification. These representative samples are insufficient to convey to one skilled in the relevant art that applicants possessed kits comprising any number of solutions comprising any or all compositions with any predetermined characteristics.

5. Claims 1-5, 7-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the predetermined characteristics recited in claim 6, does not reasonably provide enablement for any predetermined characteristic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Use of the claimed method commensurate in scope with the rejected claims would require undue experimentation on the part of one using the claimed method. Several factors are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any required experimentation is "undue." These factors include:

1) the breadth of the claims
2) the nature of the invention

3) the state of the prior art
4) the level of one of ordinary skill
5) the level of predictability in the art
6) the amount of direction provided by the inventor
7) the existence of working examples
8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims encompass any predetermined characteristics and purpose whatsoever. Consequently, the characteristics would include superconductivity, deodorizing ability, ability to form alloys, adhesiveness, curing diseases, etc. The invention involves contacting biological materials with compounds in a flow cell and separating the results of the contacting by means of ultrafiltration. The state of the prior art was such that binding between target molecules and ligands using such methods was known and that continuous flow cell cultures combined with analysis of metabolites were known. The use of a continuous flow cell and separation by ultrafiltration of the products of contacting biological samples with solutions of compounds to determine any predetermined characteristic was not known in the art. Using such a method to identify compounds with predetermined characteristics such as curing cancer or Alzheimer's Disease or regenerating a damaged spinal cord were highly unpredictable in the art. The inventors have provided working examples with respect to cytochrome P450 and bioavailability assays and assays for glutathione adduct formation. Direction has been provided with respect to biological assays such as toxicity, enzymatic activation/inactivation, and cell permeability and transport. The use of the claimed method for determining whether a compound has a predetermined characteristic other than those for which direction is provided in the specification would require experimentation. The amount of experimentation would depend upon the predetermined characteristic and associated purpose and could be quite extensive in the case of curing cancer, for example.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-6, 8, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, it is not possible to determine the metes and bounds of the term "*predetermined characteristics*." The specification provides an open definition of the term on page 3, lines 7-10 and does not provide a means of determining what "*predetermined characteristics*" can be reasonable included within the scope of the claimed invention.

B. The term "suitable" in claim 1 is a relative term which renders the claim indefinite. The term "suitable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

C. In claim 1, it is not possible to determine the metes and bounds of the term "*supportive solution*." The specification provides an open definition of the term on page 6, lines 30-31and does not provide a means of determining what solutions can be reasonable included within the scope of "*predetermined characteristics*."

D. In claim 3, it is not clear how the "*compound*" (singular) recited in the preamble can be "a combinatorial library," "a drug mixture," "a mixture of xenobiotic compounds," or "a mixture of endogenous compounds" (all pluralities). Clarification is requested.

E. In claim 4, the phrase "*capable of maintaining the biological material in a state wherein the biological material can interact with a compound in the sample*" does not allow one of ordinary skill in the art to determine the metes and bounds of the supportive solution recited in the claim. The identities of the biological material and compounds are not defined, the interaction between the biological material and compound of interest is not known, and the terms "*capable of*" and "*can interact*" leave the claim unclear with respect to whether the supportive solution does maintain the biological material or the biological material does interact with a compound in the sample. Clarification is requested.

F. In claim 5, it is not clear why "[and their metabolites]" is in brackets. Clarification is requested.

G. The term "desirable" in claim 6 is a relative term which renders the claim indefinite. The term "desirable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

H. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 8 recites the broad recitation atmospheric gasses, and the claim also recites "(oxygen and carbon dioxide) which is the narrower statement of the range/limitation.

I. In claim 12, it is not clear what is encompassed by the term "*multiple chambers with ultrafiltration.*" It appears that the word "membranes" may have been intended to follow the word "*ultrafiltration*" in the claim. Clarification is requested.

Claims Rejections – 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1-5, and 7-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Venton et al. U.S. Patent 5,872,015 February 1999.

The Venton et al. reference discloses a method for identifying a compound from a mixture of compounds that binds to a macromolecule (biological material) or macromolecular complex (abstract). The method involves the use of a device that includes an ultrafiltration membrane to retain macromolecules and bound ligands while allowing unbound compounds to pass through (abstract and column 4, lines 2-9). The biological material is held in a chamber with an inlet chamber, an outlet chamber, an ultrafiltration membrane, a solvent delivery system, an injector, and pumps (column 4, lines 2-9 and column 6, lines 32-37). Column 9, lines 51-60, disclose that loading of the macromolecule is accomplished by injection, the chamber s flushed with buffer (supportive solution), and effluent is released through an effluent port (i.e. the cell is a continuous flow cell). Column 10, lines 21-50 discloses that the a solution containing the library of test compounds is loaded into the chamber and that compounds low-affinity compounds are separated from high-affinity compounds by the continuous flow of buffer through the cell. The high-affinity compounds are dislodged from the macromolecule(s), washed from the cell through the ultrafiltration membrane, and analyzed. Present claim 1 is thus anticipated by the Venton et al. reference.

Column 19, line 43 – column 20, line 55 discloses that the macromolecules and complexes thereof may include enzymes, nucleic acids, polysaccharides, microsomes, and whole cells, anticipating present claim 2. Column 5, lines 11-32 disclose that compound libraries may be peptides, oligonucleotides, polysaccharides, small organic molecules, and molecules isolated from plant and marine sources, anticipating present claim 3. Column 9, lines 51-60 disclose that the chamber is flushed with a buffer, anticipating present claim 4. Column 10, line 21 – column 11, line 20 discloses that two buffers are used, one buffer facilitates binding (reacting) of the active compounds (ligands) to the macromolecular target and washing of non-binding compounds through the membrane, and the second buffer facilitates removal of the bound ligands from the macromolecules and their washing through the ultrafiltration membrane, anticipating present claim 5.

The method of Venton et al. includes mixing macromolecules in buffer to form a solution (stirring is disclosed in column 4, lines 10-23, for example), adequate concentrations of

macromolecule and test compounds (column 19, lines 6-42), sufficient time for the compounds to bind (column 10, lines 13-20), and temperature control (column 4, lines 23-40). The control of gasses such as oxygen and carbon dioxide are inherent the maintenance/culturing of whole cells (the use of whole cells is disclosed in column 20, line 54). Accordingly, present claim 8 is anticipated. An ultrafiltration membrane that allows test compounds to pass through but not macromolecular targets (biological samples) and mass spectrometry analysis are disclosed, for example, in the abstract, anticipating present claims 9 and 10.

The use of the Venton et al. method requires a buffer, a macromolecule in solution (biological material), an ultrafiltration membrane, and test solution containing library compounds. The use of standard compounds is inherent in the calibration of a variety of instruments used for the analysis of test compounds. Consequently, the use of the Venton et al. method inherently requires the "kit" of present claim 11.

Claims Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Venton et al. U.S. Patent 5,872,015 February 1999.

The teachings of the Venton et al. reference are described in the preceding rejections under 35 U.S.C. 102(e). The Venton et al. reference does not teach multiple chambers with ultrafiltration arranged in parallel with a single mass spectrometer.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to arrange multiple chambers with ultrafiltration (membranes) in parallel with a single mass spectrometer. One would have been motivated to do so in order to scale up the volume of samples that could be assayed at one time. One would have had a reasonable expectation for

success because high throughput mass spectrometry capable of handling large numbers of samples was routine in the art.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Thomas Prasthofer, Ph.D.

December 2, 2001 TP

BENNETT CELSA
PRIMARY EXAMINER

12/3/01